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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,679	03/11/2005	Thomas Felzmann	4518-0110PUS1	7223

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EXAMINER	
XIE, XIAOZHEN	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
09/16/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/527,679	FELZMANN, THOMAS	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,12,13 and 15-21* is/are pending in the application.

4a) Of the above claim(s) *12,13,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 17-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

The Declaration under 37 C.F.R. 1.132 of Dr. Thomas Felzmann submitted on 10 June 2008 is acknowledged. Applicant's amendment of the claims received on 10 June 2008 has been entered.

Claims 10, 11 and 14 have been cancelled. Claims 19-21 have been added in the after-Final amendment filed 9 January 2008, and have been entered in the advisory action mailed 19 February 2008. Claims 1-9, 12, 13 and 15-21 are pending. Claims 12, 13, 15 and 16 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1-9 and 17-21 are under examination.

Claim Objections/Rejections Withdrawn

The rejections of claims 1, 3-5, 9, 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Felzmann et al. (Cancer Letters, 2001, July 26, Vol. 168:145-154) ("Felzmann (2001)"), is withdrawn in response to Applicant's argument that Felzmann

(2001) does not explicitly teach loading DC with a tumor-specific antigen, instead, states "can be prepared *in principle* from any tumor".

The rejections of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Felzmann (2001), in view of Asavaroengchai et al. (PNAS, 2002, Jan. 22, Vol. 99:931-936), is withdrawn in response to Applicant's argument as above.

The rejections of claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Felzmann (2001), in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159), and further in view of Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250) ("Felzmann (2000)"), is withdrawn in response to Applicant's argument as above.

New Grounds of Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 17 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Fong et al. (Annu. Rev. Immunol., 2000, 18:245-273).

The claims are directed to a method for the treatment of a tumor which comprises (claim 17), or consisting essentially of (claim 20), administering to a patient in need thereof an effective amount of active dendritic cells (DC), wherein said active DC are tumor-specific and secrete IL-12.

Fong et al. teach using dendritic cells (DC) for cancer immunotherapy, and reviewed clinical trials using autologous DC pulsed *ex vivo* with tumor-specific antigen. Fong et al. teach that DC precursors were obtained from peripheral blood leukocyte preparations in patients with cancer, e.g., malignant B cell lymphoma, prostate caner, or melanoma, and incubated in the presence of tumor-specific antigen, e.g., tumor-specific idiotype protein (see Table 3 for antigens used in clinical trials). Fong et al. teach that during this incubation, not only the DC precursors were able to take up and process the exogenous protein, but also induced their maturation into potent APC. Fong et al. teach that the tumor-pulsed and activated DC were then administered into patient (pp. 258, see section "DC Clinical Trials"). Fong et al. also teach that the *in vivo* maturation of DC from precursor requires stimulation by one or more of stimuli, e.g., LPS, IFN-γ, IL-1β, etc. (pp. 251, Fig.. 2). Fong teaches that once activated, DC secret cytokines including IL-7 ad IL-12 (pp. 252, 2nd paragraph). Therefore, Fong et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 9, 18, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al. (Eur. J. Immunol., 2000, 30:3291-3298).

Fong et al. teach as set forth above. Fong et al., however, do not teach inducing DC maturation *in vitro* using LPS and IFN-γ.

Lopointe et al. teach that the function of dendritic cells (DC) is highly influenced by their level of maturation (see 1st paragraph in Introduction). Lopointe et al. teach that a number of clinical trials are currently in progress utilizing DC in an attempt to immunize against tumor antigens, and that optimizing DC activation, by stimulating with multiple agents, may improve current efforts towards the generation of potent T cell responses *in vivo* (see last paragraph in Discussion). Lopointe et al. teach that DC maturational signals can originate from several sources, including CD40L, IFN-γ, and lipopolysaccharides (LPS), and that immature DC *in vivo* are exposed to many of these maturational signals simultaneously or sequentially, and a combination of signals may bring about maximal T cell stimulatory capacity (2nd paragraph in Introduction). Lopointe et al. examined activation of immature DC isolated from normal donor or melanoma patient by CD40Ls, IFN-γ, and LPS, either individually or in combination, and found that while a combination of CD40Ls and LPS had a synergistic effect in increasing IL-12 secretion than treated individually, a combination of IFN-γ and LPS, or a combination of CD40Ls, IFN-γ and LPS, had the best synergistic effects in stimulating IL-12 secretion in the activated DC (pp. 3292, Fig. 1). Lopointe et al. further teach that the activated DC with higher IL-12 production (e.g., by a combination of CD40Ls and LPS) were better at

eliciting an antigen-specific T cell response compared to DC activated with only single agents. In Section 2.3, Lopointe et al. show that when autologous T cells were co-cultured with DC from metastatic melanoma patients or a normal donor pulsed with an epitope derived from the melanoma-associated antigen MART-1 (tumor antigen-pulsed DC) in the presence of CD40Ls, LPS, or a combination thereof, MART-specific reactivity (the CTL specificity) was found in CTL cultures from all seven donors in the combination treatment group, compared to three out of seven cultures showing specific reactivity in the individual treatment group. In addition, the combination treatment helped to generate better CTL in six out of seven donors when compared with DC stimulated with CD40Ls or LPS alone (Table 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fong et al., with those of Lopointe et al., to use both LPS and IFN-γ to activate DC. One of ordinary skill in the art would have been motivated to do so, because Fong et al. teach that DC pulsed with tumor-specific antigen and activated *in vivo* have a potential for cancer immunotheraoy, and have been used in clinical trials, and Lopointe et al. teach that a combination of LPS and IFN-γ induce DC to become more activated than a single stimulation, and that the more activated DC induce a better and more potent CTLs. Therefore, the teachings provide a reasonable expectation of successfully immunizing against tumor antigens in a patient.

Applicant provides Declaration under 37 C.F.R. § 1.132 by Dr. Thomas Felzmann ("Felzmann Declaration") as evidence that IL-12 secretion is limited to a

narrow time window of 24 hours following encounter of a danger signal or pathogen associated molecular patterns (PAMP), and after that, the DC go on to assume yet another functional phenotype which is mainly active in down-modulating immunity. The Felzmann Declaration states that no other investigators had considered the need to initiate the interaction of DC and T-cells early after exposure of the DC to the PAMP/danger signal in the presence of IL-12. The Felzmann Declaration states that co-stimulation is an absolute critical factor in DC dependent T-cell activation, and which makes the present invention not obvious. The Felzmann Declaration states that the dogma in immunology was, and still is, that the DC/T-cell interaction needs to be started 48 hours after delivery of the PAMP/danger signal to the DC when the expression density of co-stimulatory molecules reaches its maximum on DC membrane surface, at that time IL-12 secretion has completely ceased and it is impossible to prime killer cells against tumor antigens. The Felzmann Declaration states that a critical feature of the present invention is the fact that a short exposure of DC to a PAMP/danger signal is sufficient to initiate the differentiation program of DC, even when the stimulatory molecules are removed from the system, and inoculation into the patient need to be during the 24 hours time window in which DC secrete IL-12 and are capable of killer cell priming.

The Felzmann Declaration further states that LPS represents bacterial endotoxin and is the substance responsible for lethal endotoxin shocks during a bacterial sepsis, and therefore, the use of LPS as a PAMP to initiate DC differentiation/maturation was considered impossible because of the related potential for adverse events. The

Felzmann Declaration states that only their later experiments indicated that it is feasible to use bacterial endotoxin as a PAMP to deliver a differentiation/maturation signal to DCs.

The Declaration of Dr. Thomas Felzmann under 37 C.F.R. § 1.132 filed 10 June 2008 has been considered, but is insufficient to overcome the rejection under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al., as set forth above for the following reasons.

Fong et al. reviewed a number of clinical trials using autologous DC isolated from cancer patients, pulsed *ex vivo* with different tumor antigen, and activated *in vitro* with different maturation protocols. Many of these clinical trials have demonstrated efficacy. For example, in the DC trial for B cell lymphoma, two of the patients experienced complete tumor regression, including one entered the trial with bulky disease and remain in complete remission for more than three years (pp. 259, last paragraph). Also, one complete response was reported in a cohort of six patients in a DC trial for melanoma (pp. 260, 2nd full paragraph). Therefore, no matter what kinds of DC preparation method and treatment regime were used, it has proved to be working.

Further, the claims have no limitation regarding the time window for inoculation into the patient. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

With regard to the use of LPS would impose the related potential for adverse events, in describing the protocol for DC preparation, Fong et al. states that after the

incubation (pulsing and activating step), the DC were extensively washed to remove free protein, resuspended in sterile saline, and administered to the patients by intravenous infusion (pp. 259, top paragraph). Therefore, only the Dc, but not free protein, are administered to patients.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al., and further in view of Asavaroengchai et al. (PNAS, 2002, Jan. 22, Vol. 99:931-936, reference provided previously).

Fong et al and Lopointe et al. teach as set forth above. They, however, do not teach that the treatment is performed after bone marrow transplantation (claim 2).

Asavaroengchai et al. teach that bone marrow transplants (BMT) or peripheral stem cell transplants are currently being used for the treatment of hematopoietic and solid tumors, and combining suitable immunization approaches with BMT can overcome tumor induced defects in the host anti-tumor immune response. Asavaroengchai et al. teach that in a therapeutic setting tumor antigen-pulsed DCs can have an impact on residual tumor that remains following BMT (pp. 931, see Abstract and Introduction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fong et al., and Lopointe et al., with those of Asavaroengchai et al., to perform the treatment after bone marrow transplantation. One of ordinary skill in the art would have been motivated to combine the teachings, because Fong et al. and Lopointe et al. teach a method of immunotherapy using tumor antigen pulsed DC that release IL-12 upon maturation with

LPS and IFN-γ, Asavaroengchai et al. teach that tumor-pulsed DC can have impact on residual tumor that remains following BMT. Therefore, the teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Claims 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fong et al., in view of Lopointe et al., and further in view of Rieser (Urol. Int., 1999, Vol. 63(3):151-159, reference provided previously) and Felzmann et al. (Cancer Letters, 2000, Vol. 161:241-250) ("Felzmann (2000)", reference provided previously).

Fong et al. and Lopointe et al. teach as set forth above. They, however, do not teach that the DC are additionally charged with a tracer antigen (claim 6) that is keyhole limpet hemocyanine (KLH) (claim 7), or additionally charged with an adjuvant tetanus toxoid (claim 8).

Rieser teaches using KLH as a tracer molecule for the determination of the magnitude, kinetics, and T-helper type-1 bias of the cellular and humoral immune response induced by DC-based immunization (pp. 151, see Abstract).

Felzmann (2000) teaches Xenogenization by tetanus toxoid (TT) loading into human tumor cells for anti-tumor immune therapy (pp. 241, Abstract). Felzmann (2000) teaches that unresponsiveness to tumor associated antigens (TAAs) could be overcome when a mixture of TAAs was used together with class II restricted peptides from TT for cell pulsing in vitro (pp. 241, Introduction, 1st paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Fong et al. and Lopointe et al., with those of Rieser and Felzmann (2000), to additionally load DC with a tracer antigen KLH and an adjuvant tetanus toxoid. One of ordinary skill in the art would have been motivated to combine the teachings, because Fong et al. and Lopointe et al. teach a method of immune therapy using tumor antigen pulsed DC that release IL-12 upon maturation with LPS and IFN-γ, Rieser teaches using KLH as a tracer molecule for determination of the kinetics of the immune therapy, and Felzmann (2000) teaches tetanus toxoid (TT) loading into human tumor cells enhances responsiveness to tumor associated antigens. Therefore, the teachings provide a reasonable expectation of successfully treating a tumor in a patient.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
September 3, 2008

/Elizabeth C. Kemmerer/

Primary Examiner, Art Unit 1646